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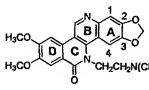
(54) Title: NITRO AND AMINO SUBSTITUTED TOPOISOMERASE AGENTS



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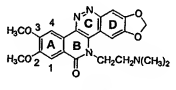

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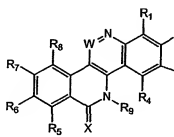

(I)

(57) Abstract: The invention provides compounds of formula 1 : wherein R_1-R_9, W, and X have any of the meanings defined in the specification and their pharmaceutically acceptable salts. The invention also provides pharmaceutical compositions comprising a compound of formula 1, processes for preparing compounds of formula 1, intermediates useful for preparing compounds of formula 1, and therapeutic methods for treating cancer using compounds of formula 1.

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NITRO AND AMINO SUBSTITUTED TOPOISOMERASE AGENTS

Priority of Invention

This application claims priority to United States Provisional Patent Application Number 60/402167, filed 09 August 2002.

Government Funding

The invention described herein was made with government support under Grant Numbers CA39662 and CA077433 from the National Cancer Institute. The United States Government has certain rights in the invention.

Background of the Invention

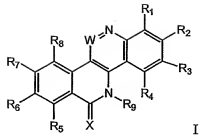
DNA-topoisomerases are enzymes which are present in the nuclei of cells where they catalyze the breaking and rejoining of DNA strands, which control the topological state of DNA. Recent studies also suggest that topoisomerases are also involved in regulating template supercoiling during RNA transcription. There are two major classes of mammalian topoisomerases. DNA-topoisomerase-I catalyzes changes in the topological state of duplex DNA by performing transient single-strand breakage-union cycles. In contrast, mammalian topoisomerase II alters the topology of DNA by causing a transient enzyme bridged double-strand break, followed by strand passing and resealing. Mammalian topoisomerase II has been further classified as Type II α and Type II β. The antitumor activity associated with agents that are topoisomerase poisons is associated with their ability to stabilize the enzyme-DNA cleavable complex. This drug-induced stabilization of the enzyme-DNA cleavable complex effectively converts the enzyme into a cellular poison.

Several antitumor agents in clinical use have potent activity as mammalian topoisomerase II poisons. These include adriamycin, actinomycin D, daunomycin, VP-16, and VM-26 (teniposide or epipodophyllotoxin). In contrast to the number of clinical and experimental drugs which act as

topoisomerase II poisons, there are currently only a limited number of agents which have been identified as topoisomerase I poisons. Camptothecin and its structurally-related analogs are among the most extensively studied topoisomerase I poisons. Recently, bi- and terbenzimidazoles (Chen et al., *Cancer Res.* **1993**, *53*, 1332-1335; Sun et al., *J. Med. Chem.* **1995**, *38*, 3638-3644; Kim et al., *J. Med. Chem.* **1996**, *39*, 992-998), certain benzo[c]phenanthridine and protoberberine alkaloids and their synthetic analogs (Makhey et al., *Med. Chem. Res.* **1995**, *5*, 1-12; Janin et al., *J. Med. Chem.* **1975**, *18*, 708-713; Makhey et al., *Bioorg. & Med. Chem.* **1996**, *4*, 781-791), as well as the fungal metabolites, bulgarein (Fujii et al., *J. Biol. Chem.* **1993**, *268*, 13160-13165) and saintopin (Yamashita et al., *Biochemistry* **1991**, *30*, 5838-5845) and indolocarbazoles (Yamashita et al., *Biochemistry* **1992**, *31*, 12069-12075) have been identified as topoisomerase I poisons. Other topoisomerase poisons have been identified including certain benzo[i]phenanthridine and cinnoline compounds (see LaVoie et al., U.S. Patent No. 6,140,328 and WO 01/32631). Despite these reports there is currently a need for additional agents that are useful for treating cancer.

Summary of the Invention

Applicant has discovered compounds that show inhibitory activity against topoisomerase I and/or topoisomerase II, and compounds that are effective cytotoxic agents against cancer cells, including drug-resistant cancer cells. Accordingly, the invention provides a compound of the invention which is a compound of formula I:



I

wherein:

one of R_1, R_2, R_3, and R_4 is nitro or NR_aR_b;

and the remaining R_1, R_2, R_3, and R_4 are each independently hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, NR_aR_b, $COOR_c$, OR_d; or R_1 and R_2, R_2 and R_3, or R_3 and R_4 taken together are methylenedioxy, 1,2-ethylenedioxy, or 1,3-propylenedioxy;

R_5 is hydrogen, hydroxy, or fluoro;

each R_6, R_7, and R_8 is independently hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, NR_aR_b, $COOR_c$, OR_d; or R_6 and R_7, or R_7 and R_8 taken together are methylenedioxy, 1,2-ethylenedioxy, or 1,3-propylenedioxy;

R_9 is $(C_1\text{-}C_6)$alkyl substituted with one or more (e.g. 1, 2, 3, or 4) solubilizing groups R_z;

W is N or CH;

X is two hydrogens, =O, =S, or $=NR_e$;

R_a and R_b are each independently hydrogen or $(C_1\text{-}C_6)$alkyl, or R_a and R_b together with the nitrogen to which they are attached form a pyrrolidino, piperidino or morpholino ring;

each R_c is hydrogen, $(C_1\text{-}C_6)$alkyl, aryl, or aryl$(C_1\text{-}C_6)$alkyl;

each R_d is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkanoyl, aryl, or aryl$(C_1\text{-}C_6)$alkyl; and R_e is hydrogen, $(C_1\text{-}C_6)$alkyl, aryl, or aryl$(C_1\text{-}C_6)$alkyl;

or a pharmaceutically acceptable salt thereof.

The invention also provides a pharmaceutical composition comprising a effective amount of a compound of the invention in combination with a pharmaceutically acceptable diluent or carrier.

The invention also provides a method of inhibiting cancer cell growth, comprising administering to a mammal afflicted with cancer, an amount of a compound of the invention, effective to inhibit the growth of said cancer cells.

The invention also provides a method comprising inhibiting cancer cell growth by contacting said cancer cell *in vitro* or *in vivo* with an amount of a compound of the invention, effective to inhibit the growth of said cancer cell.

The invention also provides a compound of the invention for use in medical therapy, preferably for use in treating cancer, for example, solid tumors, as well as the use of a compound of the invention for the manufacture of a medicament useful for the treatment of cancer, for example, solid tumors.

The invention also provides processes and novel intermediates disclosed herein which are useful for preparing compounds of the invention. Some of the compounds of formula I are useful to prepare other compounds of formula I.

Brief Description of the Figures

Figure 1	shows the structure of compounds **1** and **2**.
Figure 2	shows the structure of representative compounds of formula I (**3a-3d** and **4a-4d**) and the structure of compound **5**
Figure 3	illustrates the synthesis of representative compounds of formula I (**3a-3d** and **4a-4d**) and compound **5**.
Figure 4	illustrates the synthesis of a representative compound of formula I (**12a**) and compound (**12b**)

Detailed Description

The following definitions are used, unless otherwise described.

"(C_1-C_6)alkyl" denotes both straight and branched carbon chains with 1, 2, 3, 4, 5, or 6, carbon atoms, but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to.

"(C_3-C_6)cycloalkyl" denotes a carbocyclic ring with 3, 4, 5, or 6, carbon atoms.

"Aryl" denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic. Examples of aryl include phenyl, indenyl, and naphthyl.

"Aryl(C_1-C_6)alkyl" refers to a group of the formula aryl-(C_1-C_6)alkyl-, where aryl and (C_1-C_6)alkyl are as defined herein.

"Solubilizing group (R_z)" is a substituent that increases the water solubility of the compound of formula I compared to the corresponding compound lacking the R_z substituent (i.e. wherein R_z is hydrogen). Examples of solubilizing groups include (C_1-C_6)alkoxycarbonyl (e.g. -CO_2Me), cyano, halo, hydroxy, mercapto, oxo (=O), carboxy (COOH), nitro, pyrrolidinyl, piperidinyl, imidazolidinyl, imidazolinyl, piperazinyl, morpholinyl, thiomorpholinyl, and –NR_fR_g, wherein R_f and R_g may be the same or different and are chosen from hydrogen, (C_1-C_6)alkyl, and (C_3-C_6)cycloalkyl.

Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

A specific value for W is N.

Another specific value for W is CH.

A specific value for R_1 is nitro.

Another specific value for R_1 is NR_aR_b.

A specific compound is a compound wherein R_2, R_3, and R_4 are each independently hydrogen, or OR_d, wherein each R_4 is hydrogen or (C_1-C_6)alkyl.

A specific compound is a compound wherein R_2, R_3, and R_4 are each hydrogen.

A specific value for R_2 is nitro or NR_aR_b.

Another specific value for R_2 is nitro.

Another specific value for R_2 is NR_aR_b.

A specific compound is a compound wherein R_1, R_3, and R_4 are each independently hydrogen, or OR_d, wherein each R_4 is hydrogen or (C_1-C_6)alkyl.

A specific compound is a compound wherein R_1, R_3, and R_4 are each hydrogen.

A specific value for R_3 is nitro or NR_aR_b.

Another specific value for R_3 is nitro.

Another specific value for R_3 is NR_aR_b.

A specific compound is a compound wherein R_1, R_2, and R_4 are each independently hydrogen, or OR_d, wherein each R_4 is hydrogen or (C_1-C_6)alkyl.

A specific compound is a compound wherein R_1, R_2, and R_4 are each hydrogen.

A specific compound is a compound wherein R_2 or R_3 is nitro or NR_aR_b.

A specific value for R_4 is nitro.

Another specific value for R_4 is NR_aR_b.

A specific compound is a compound wherein R_1, R_2, and R_3 are each independently hydrogen, or OR_d, wherein each R_4 is hydrogen or (C_1-C_6)alkyl.

A specific compound is a compound wherein R_1, R_2, and R_3 are each hydrogen.

A specific value for R_5 is hydrogen.

Another specific value for R_5 is hydroxy or fluoro.

A specific compound is a compound wherein each R_6, R_7, and R_8 is independently hydrogen, or OR_d.

A specific compound is a compound wherein R_6 and R_7 are each independently OR_d, wherein each R_d is $(C_1\text{-}C_6)$alkyl; and R_8 is hydrogen.

A specific compound is a compound wherein or R_6 and R_7 taken together are methylenedioxy, 1,2-ethylenedioxy, or 1,3-propylenedioxy; and R_8 is hydrogen.

A specific value for R_9 is $(C_1\text{-}C_6)$alkyl substituted with one or more hydroxy groups.

Another specific value for R_9 is $(C_1\text{-}C_6)$alkyl substituted with one hydroxy group.

Another specific value for R_9 is $(C_1\text{-}C_6)$alkyl substituted with one or more mercapto groups.

Another specific value for R_9 is $(C_1\text{-}C_6)$alkyl substituted with one mercapto group.

Another specific value for R_9 is $(C_1\text{-}C_6)$alkyl substituted with one or more carboxy groups.

Another specific value for R_9 is $(C_1\text{-}C_6)$alkyl substituted with one carboxy group.

Another specific value for R_9 is $(C_1\text{-}C_6)$alkyl substituted with one or more NR_fR_g groups.

Another specific value for R_9 is $(C_1\text{-}C_6)$alkyl substituted with one NR_fR_g group.

Another specific value for R_9 is $(C_1\text{-}C_6)$alkyl substituted with one or more NH_2 groups.

Another specific value for R_9 is a $(C_1\text{-}C_6)$alkyl substituted with one NH_2 group.

Another specific value for R_9 is $(C_1\text{-}C_6)$alkyl substituted with one or more $N(CH_3)_2$ groups.

Another specific value for R_9 is a (C_1-C_6)alkyl substituted with one $N(CH_3)_2$ group.

Another specific value for R_9 is (C_1-C_6)alkyl substituted with one or more $N(CH_2CH_3)_2$ groups.

Another specific value for R_9 is a (C_1-C_6)alkyl substituted with one $N(CH_2CH_3)_2$ group.

Another specific value for R_9 is a (C_1-C_6)alkyl substituted with one or more (C_1-C_6)alkoxycarbonyl, cyano, halo, hydroxy, mercapto, oxo, carboxy, nitro, pyrrolidinyl, piperidinyl, imidazolidinyl, imidazolinyl, piperazinyl, morpholinyl, thiomorpholinyl, or $-NR_fR_g$ groups.

Another specific value for R_9 is a (C_2-C_4)alkyl substituted with one or two groups selected from hydroxy, mercapto, carboxy, amino, methylamino, ethylamino, dimethylamino, and diethylamino.

Another specific value for R_9 is 2-hydroxyethyl.

Another specific value for R_9 is 3-hydroxypropyl.

Another specific value for R_9 is 2-hydroxypropyl.

Another specific value for R_9 is $-CH_2CH_2-NR_fR_g$ wherein R_f and R_f are each independently hydrogen or (C_1-C_6)alkyl.

Another specific value for R_9 is $-CH_2CH_2-NR_fR_g$ wherein R_f and R_f are each independently methyl or ethyl.

A specific compound is any one of compounds **3a**, **3b**, **3c**, **4a**, **4b**, **4c**, and **12a**; or a pharmaceutically acceptable salt thereof.

Another specific compound is a compound of formula (I) wherein R_1 is hydrogen; R_2 is hydrogen; R_3 is nitro; R_4 is hydrogen; R_5 is hydrogen; R_6 is methoxy; R_7 is methoxy; R_8 is hydrogen; and R_9 is 2-(*N*,*N*-dimethylamino)ethyl or 2-(*N*,*N*-diethylamino)ethyl; W is N or CH; and X is =O; or a pharmaceutically acceptable salt thereof.

A compound of formula I can be prepared as described in the Examples below and as illustrated in Figure 3. Displacement of chloride from **6a**-**6e** with the requisite amine provides compounds **7a**-**7e**. Amide formation provides

compounds **8a-8e**, which can be cyclized to provide compounds **3a-3d** and **5**. Subsequent reduction of the nitro group in compounds **3a-3d** provides amines **4a-4d**.

A compound of formula I can also be prepared as described in Figure 4. Displacement of chloro or methoxy from **9a** and **9b** with the requisite amine provides compounds **10a** and **10b**. Amide formation provides compounds **11a** and **11b**, which can be cyclized to provide compounds **12a** and **12b**.

The starting materials employed in the synthetic methods described herein are commercially available, have been reported in the scientific literature, or can be prepared from readily available starting materials using procedures known in the field. It may be desirable to optionally use a protecting group during all or portions of the above described synthetic procedures. Such protecting groups and methods for their introduction and removal are well known in the art. See Greene, T.W.; Wutz, P.G.M. "Protecting Groups In Organic Synthesis" second edition, 1991, New York, John Wiley & Sons, Inc.

It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine topoisomerase inhibition activity or cytotoxic activity using the standard tests described herein, or using other similar tests which are well known in the art.

In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid

addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α-ketoglutarate, and α-glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal, for example, sodium, potassium or lithium, or alkaline earth metal, for example calcium, salts of carboxylic acids can also be made.

The compounds of formula I can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, that is, orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

Thus, the present compounds may be systemically administered, for example, orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin;

excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form must be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene

glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Examples of useful dermatological compositions which can be used to deliver the compounds of formula I to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

Useful dosages of the compounds of formula I can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

Generally, the concentration of the compound(s) of formula I in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.

The amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

In general, however, a suitable dose will be in the range of from about 0.5 to about 100 mg/kg per day, e.g., from about 1 to about 60 mg/kg of body weight per day or about 2 to 50 mg/kg per day.

The compound may conveniently be administered in unit dosage form; for example, containing 5 to 1,000 mg, conveniently 10 to 750 mg, most conveniently, 50 to 500 mg of active ingredient per unit dosage form.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g.,

into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

The ability of a compound of the invention to effect topoisomerase I or II mediated DNA cleavage can be determined using pharmacological models that are well known to the art, for example, using a model like Test A described below.

Test A. **Topoisomerase-mediated DNA cleavage assays**

Human topoisomerase I was expressed in *E. Coli* and isolated as a recombinant fusion protein using a T7 expression system as described by Gatto, B., et al., *Cancer Res.* **1996**, *56*, 2795-2800. Plasmid YepG was purified by the alkali lysis method followed by phenol deproteination and CsCl/ethidium isopycnic centrifugation method as described by Maniatis, T., et al., J. *Molecular Cloning, a Laboratory Manual*; Cold Spring Harbor Laboratory: Cold Spring Harbor, NY 1982; pp 149-185. The end-labeling of the plasmid was accomplished by digestion with a restriction enzyme followed by end-filling with Klenow polymerase as previously described by Tewey, K.M., et al., *Science* **1984**, *226*, 466-468. The cleavage assays were performed as previously reported (see Gatto, B. , et al., *Cancer Res.* **1996**, *56*, 2795-2800; and Wang, H., et al., *Biochemistry* **2001**, *40*; 3316-3323) . The drug and the DNA in presence of topoisomerase I was incubated for 30 minutes at 37 °C. The reactions were terminated by the addition of 5 µl of 5% SDS and 1 mg/ml protein kinase K with an additional 1 hour of incubation at 37 °C. Samples were then alkali denatured by the addition of NaOH, EDTA, sucrose, and bromophenol blue to final concentrations of 75 mM, 2.5%, and 0.05 mg/ml, respectively, prior to loading onto a neutral agarose gel. After development of the gels, typically 24-hour exposure was used to obtain autoradiograms outlining the extent of DNA fragmentation. Topoisomerase I-mediated DNA cleavage

values are reported as REC, Relative Effective Concentration, i.e. concentrations relative to topotecan, whose value is arbitrarily assumed as 1.0, that are able to produce the same cleavage on the plasmid DNA in the presence of human topoisomerase I. Data for representative compounds of the invention is provided in Table 1 below.

The cytotoxic effects of a compound of the invention can be determined using pharmacological models that are well known to the art, for example, using a model like Test B described below.

Test B. **Inhibition of Cell Growth: MTT-microtiter plate tetrazolinium cytotoxicity assay (RPMI 8402, CPT-K5, U937, U937/CR Cells)**

The cytotoxicity was determined using the MTT-microtiter plate tetrazolinium cytotoxicity assay (MTA – See Mosmann, T., *J. Immunol. Methods* **1983**, *65*, 55-63; Carmichael, J., et al., *Cancer Res.* **1987**, *47*, 936-942; and Denizot, F., et al., *J. Immunol. Methods* **1986**, *89*, 271-277). The human lymphoblast RPMI8402 and its camptothecin-resistant variant cell line, CPT-K5 were provided by Dr. Toshiwo Andoh (Aichi Cancer Center Research Institute, Nagoya, Japan – See Andoh, T. , et al., *Adv. in Pharmacology* **1994**, *29B*, 93-103). The cytotoxicity assay was performed using 96-well microtiter plates. Cells were grown in suspension at 37 °C in 5% CO_2 and maintained by regular passage in RPMI medium supplemented with 10% heat- inactivated fetal bovine serum, L-glutamine (2 mM), penicillin (100 U/mL), and streptomycin (0.1 mg/mL). Each well was plated with either 2,000 RPMI8402 cells or 4,000 CPT-K5 cells. For determination of IC_{50}, cells were exposed continuously for 4 days to varying concentrations of drug, and MTT assays were performed at the end of the fourth day. Each assay was performed with a control that did not contain any drug. All assays were performed at least twice in 6 replicate wells. Data for representative compounds is provided in Table 1 below.

Table 1. TOP1-targeting Activity and Cytotoxicity Data

Compound	TOP1-mediated[a] DNA Cleavage	Cytotoxicity IC_{50} (μM)[b]			
		RPMI 8402	CPT-K5	P388	P388/CPT45
1	0.5	0.002	0.9	0.001	0.23
2	0.3	0.001	0.6	0.002	0.36
3a	9	0.22	3.0	0.19	2.1
3b	6	0.075	3.35	0.03	0.34
3c	2	0.018	0.8	0.04	0.2
3d	>300	5.5	11.5	6.0	7.0
4a	100	0.65	2.0	0.35	0.21
4b	12	0.1	2.1	0.06	0.23
4c	6	0.04	1.35	0.02	0.33
4d	> 300	4.0	8.0	3.0	3.5
5	10	0.1	1.65	0.07	0.30
12a		0.003	3.3		
12b		0.018	1.5		
CPT	0.2	0.005	61	0.009	>10
CPT-11	25	0.57	>100	2.0	>10
Topotecan	1	0.012	> 50	0.035	>10
VM-26		0.22	0.28		

[a]Topoisomerase I cleavage values are reported as REC, relative effective concentration, i.e., concentrations relative to topotecan (TPT), whose value is arbitrarily assumed as 1, that are able to produce the same cleavage on the plasmid DNA in the presence of human TOP1.
[b]IC_{50} has been calculated after 4 days of continuous drug exposure.

The compounds of the invention can function as cytotoxic agents against tumor cell lines, including multi-drug resistant tumor cell lines. Thus, the compounds are useful to treat cancer and can be used to treat tumors that are resistant to other specific chemotherapeutic agents.

Topoisomerase inhibitors are also known to possess antibacterial, antifungal, antiprotozoal, antihelmetic, antipsoriatic, and antiviral activity. Accordingly, the topoisomerase inhibitors of the invention may also be useful as antibacterial, antifungal, antiprotozoal, antihelmetic, antipsoriatic, antipsoriatic, or antiviral agents. In particular, compounds of the invention that demonstrate little or no activity as mammalian topoisomerase I poisons, because of the possibility of similar molecular mechanism of action, could be highly active and selective antibacterial, antifungal, antiprotozoal, antihelmetic, antipsoriatic, or

antiviral agents. Thus, certain compounds of the invention may be particularly useful as systemic antibacterial, antifungal, antiprotozoal, antihelmetic, antipsoriatic, or antiviral agents in mammals. The invention also provides the use of a compound of the invention for the manufacture of a medicament useful for producing an antibacterial, antifungal, antiprotozoal, antihelmetic, antipsoriatic, antipsoriatic, antipsoriatic, or antiviral effect in a mammal.

As used herein, the term "solid mammalian tumors" include cancers of the head and neck, lung, mesothelioma, mediastinum, esophagus, stomach, pancreas, hepatobiliary system, small intestine, colon, rectum, anus, kidney, ureter, bladder, prostate, urethra, penis, testis, gynecological organs, ovarian, breast, endocrine system, skin central nervous system; sarcomas of the soft tissue and bone; and melanoma of cutaneous and intraocular origin. The term "hematological malignancies" includes childhood leukemia and lymphomas, Hodgkin's disease, lymphomas of lymphocytic and cutaneous origin, acute and chronic leukemia, plasma cell neoplasm and cancers associated with AIDS. The preferred mammalian species for treatment are humans and domesticated animals.

The invention will now be illustrated by the following non-limiting Examples.

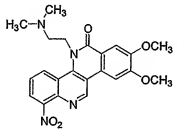
Examples

General Experimental

Melting points were determined with a Thomas-Hoover Unimelt capillary melting point apparatus. Column chromatography refers to flash chromatography conducted on SiliTech 32-63 μm, (ICN Biomedicals, Eschwegge, Ger.) using the solvent systems indicated. Infrared spectral data (IR) were obtained on a Perkin-Elmer 1600 Fourier transform spectrophotometer and are reported in cm^{-1}. Proton (^1H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance were recorded on a Varian Gemini-200 Fourier Transform spectrometer. NMR spectra (200 MHz ^1H and 50 MHz ^{13}C) were recorded in

the deuterated solvent indicated with chemical shifts reported in δ units downfield from tetramethylsilane (TMS). Coupling constants are reported in hertz (Hz). Mass spectra were obtained from Washington University Resource for Biomedical and Bio-organic Mass Spectrometry within the Department of Chemistry at Washington University, St. Louis, MO.

Example 1: 8,9-Dimethoxy-1-nitro-5-[2-(N,N-dimethylamino)ethyl]-5*H*-dibenzo[*c,h*][1,6]naphthyridin-6-one (3a).



A mixture of compound **8a** (660 mg, 1.2 mmol), $Pd(OAc)_2$ (54 mg, 0.024 mmol), P(*o*-tolyl)$_3$ (147 mg, 0.048 mmol), and Ag_2CO_3 (660 mg, 2.4 mmol) in DMF (36 mL) was heated to reflux and stirred for 30 minutes. The reaction mixture was cooled, diluted with chloroform and filtered through Celite, and the solvent was removed under vacuum. The crude residue was chromatographed in 98:2 chloroform-methanol, to provide 190 mg of the cyclized product, in 36% yield; m.p. = 257-258° C; ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 6H), 3.01 (t, 2H, *J*=6.9 Hz), 4.09 (s, 3H), 4.13 (s, 3H), 4.70 (t, 2H, *J*=6.9 Hz), 7.67 (dd, 1H, *J*=9.0, *J*=7.7), 7.72 (s, 1H), 7.92 (s, 1H), 7.99 (dd, 1H, *J*=7.7, *J*=1.1), 8.80 (dd, 1H, *J*=9.0, *J*=1.1), 9.68 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 45.9, 49.4, 56.4, 56.5, 57.8, 102.2, 108.9, 113.0, 120.0, 120.2, 122.5, 124.5, 126.8, 128.4, 140.1, 140.6, 147.7, 149.5, 151.2, 154.6, 163.5; IR ($CHCl_3$) 1347, 1536, 1657; HRMS calcd for $C_{22}H_{22}O_5N_4H$: 423.1668; found: 423.1650.

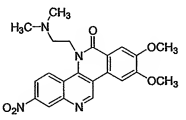
The intermediate compound **8a** was prepared as follows.

a. **4-Chloro-8-nitroquinoline (6a).** This intermediate was prepared from 4-chloroquinoline (obtained by treating 4-hydroxyquinoline with $POCl_3$ as described by Gouley, R.W., et al., *J. Amer. Chem. Soc.*, 1947, *69*, 303-306. 4-Chloroquinoline (10.0 g, 61.3 mmol) was added in small portions to sulfuric acid (45 mL) taking care to maintain the temperature at or below 15° C. Then the solution was cooled and maintained at -15° C during the addition of fuming nitric acid (9 mL). The mixture was allowed to warm to room temperature and stirred for an additional 3 hours. The reaction mix was poured on ice and basified (pH 9) with NH_4OH. The resulting precipitate was filtered, washed well with water, dried, and recrystallized from methanol to provide 7.5 g of **6a**, in 59 % yield; m.p. = 128-129° C (lit. m.p. = 129-130° C); ^1H NMR ($CDCl_3$) δ 7.67 (d, 1H, J=4.5), 7.75 (dd, 1H, J=8.6 Hz, J=7.6), 8.10 (dd, 1H, J=7.6, J=1.3), 8.48 (dd, 1H, J=8.6, J=1.3), 8.94 (d, 1H, J=4.5); ^{13}C NMR ($CDCl_3$) δ 123.0, 124.4, 126.5, 127.5, 128.3, 140.6, 143.2, 148.7, 152.1.

b. **N'-(8-Nitroquinolin-4-yl)-N,N-dimethylethane-1,2-diamine (7a).** Compound **6a** (1.0 g, 4.8 mmol) was heated to reflux in N,N-dimethylethylenediamine (6.25 g, 70.9 mmol) with stirring for 2h, then cooled and the solvent was evaporated *in vacuo*. The crude residue was dissolved in 5 % aqueous HCl (150 mL) and washed with chloroform (3 x 100mL), and then basified with 30 % NaOH, extracted into chloroform (5 x 100 mL), dried ($MgSO_4$), evaporated, and chromatographed in 98:2 chloroform-methanol, to provide 480 mg, in 44 % yield; m.p. = 78-79° C; ^1H NMR ($CDCl_3$) δ 2.34 (s, 6H), 2.71 (t, 2H, J=5.9 Hz), 3.31 (m, 2H), 6.17 (br, 1H), 6.45 (d, 1H, J=5.3), 7.42 (dd, 1H, J=8.4, J=7.7), 7.87 (dd, 1H, J=7.6, J=1.4), 8.01 (dd, 1H, J=8.4, J=1.4), 8.61 (d, 1H, J=5.3); ^{13}C NMR ($CDCl_3$) δ 39.9, 45.1, 56.9, 100.2, 120.4, 122.7, 123.0, 124.1, 140.3, 149.0, 149.8, 153.1; IR ($CHCl_3$) 1363, 1533, 3384.

c. **N-(8-Nitroquinolin-4-yl)-N-(N,N-dimethylaminoethyl)-2-iodo-5,6-dimethoxybenzamide (8a).** Oxalyl chloride (762 mg, 6.0 mmol) was added to a solution of 3,4-dimethoxy-6-iodobenzoic acid (570 mg, 1.85 mmol) in anhydrous methylene chloride (20 mL), and the stirred mixture was refluxed for 3 hours. The mixture was then concentrated to dryness under reduced pressure. The acid chloride was redissolved in 20 mL of anhydrous methylene chloride, and this solution was added to a solution of 7a (400 mg, 1.54 mmol) and triethylamine (1.14 g, 11.3 mmol) in methylene chloride (20 mL), and the resulting mixture was stirred at reflux overnight. The reaction mix was cooled and washed with saturated sodium bicarbonate (3 x 75 mL), and extracted with 5 % aqueous HCl (4 x 100 mL). The combined aqueous extracts were basified with 30% NaOH and then extracted with chloroform (3 x 100 mL). Combined organic extracts were then dried ($MgSO_4$) and evaporated to give 722 mg of the amide, in 85 % yield; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 6H), 2.69 (m, 2H), 3.32 (s, 3H), 3.74 (s, 3H), 3.95 (m, 1H), 4.57 (m, 1H), 6.41 (s, 1H), 7.02 (s, 1H), 7.75 (m, 2H), 8.05 (d, 1H, *J*=6.6), 8.44 (d, 1H, *J*=8.4), 8.95 (d, 1H, *J*=4.4); ^{13}C NMR ($CDCl_3$) δ 45.4, 47.3, 55.7, 56.1, 56.5, 82.7, 110.7, 121.9, 123.3, 124.0, 126.1, 126.9, 127.2, 133.1, 140.9, 147.4, 148.4, 149.0, 150.1, 153.0, 169.9; IR ($CHCl_3$) 1362, 1536, 1655.

Example 2: 8,9-Dimethoxy-2-nitro-5-[2-(N,N-dimethylamino)ethyl]-5*H*-dibenzo[*c*,*h*][1,6]naphthyridin-6-one (3b).



A mixture of compound **8b** (660 mg, 1.2 mmol), $Pd(OAc)_2$ (54 mg, 0.024 mmol), P(*o*-tolyl)$_3$ (147 mg, 0.048 mmol), and Ag_2CO_3 (660 mg, 2.4 mmol) in DMF (36 mL) was heated to reflux and stirred for 6 hours, and then an equal amount of $Pd(OAc)_2$ (54 mg, 0.024 mmol) and P(*o*-tolyl)$_3$ were stirring was continued for an additional 12 hours. The reaction mixture was cooled, diluted with chloroform and filtered through Celite, and the solvent was removed under vacuum. The crude residue was chromatographed in 98:2 chloroform-methanol, to provide 65 mg of the cyclized product, in 12 % yield; m.p. = 214-217° C; ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 6H), 3.04 (t, 2H, *J*=7.0 Hz), 4.10 (s, 3H), 4.17 (s, 3H), 4.69 (t, 2H, *J*=7.0 Hz), 7.77 (s, 1H), 8.00 (s, 1H), 8.37 (dd, 1H, *J*=9.5, *J*=2.4), 8.82 (d, 1H, *J*=9.5), 9.06 (d, 1H, *J*=2.4), 9.72 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 45.9, 49.4, 56.5, 56.5, 57.9, 97.2, 102.4, 109.0, 113.8, 119.1, 120.4, 122.6, 126.3, 126.7, 140.6, 147.2, 147.9, 148.0, 151.4, 154.5, 163.5; IR ($CHCl_3$) 1343, 1536, 1654; HRMS calcd for $C_{22}H_{22}O_5N_4H$: 423.1668; found: 423.1684.

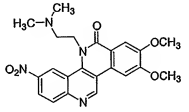
The intermediate compound **8b** was prepared as follows.

a. 4-Chloro-7-nitroquinoline (6b). 4-Chloro-7-nitro was prepared from 4-hydroxy-7-nitroquinoline[2]. 4-Hydroxy-7-nitroquinoline (3.5 g, 18.4 mmol) was refluxed in $POCl_3$ (15 mL) for 1 hour. The reaction mix was cooled and $POCl_3$ was removed on the rotavap. Water (50 mL) was added to the crude product, and after any residual $POCl_3$ had been hydrolyzed, the mixture was made basic (pH 9) using NH_4OH and extracted into chloroform (5 x 100 mL), washed with water (3 x 100 mL), dried ($MgSO_4$), and the solvent evaporated *in vacuo*, to give 2.4 g of the chloroquinoline, in 63 % yield; m.p. = 166-167° C (lit. m.p. = 156-160° C); ^{1}H NMR ($CDCl_3$) δ 7.71 (d, 1H, *J*=4.7), 8.44 (m, 2H), 8.98 (d, 1H, *J*=4.7), 9.06 (d, 1H, *J*=1.4); ^{13}C NMR ($CDCl_3$) δ 121.1, 124.0, 126.0, 126.4, 129.1, 133.7, 143.2, 148.1, 152.2.

b. **N'-(7-Nitroquinolin-4-yl)-N,N-dimethylethane-1,2-diamine (7b).** Compound **6b**(1.9 g, 9.1 mmol) was heated to reflux in N,N-dimethylethylenediamine (12.5 g, 141.5 mmol) with wtirring for 2h, then cooled and the solvent was evaporated *in vacuo*. The crude residue was dissolved chloroform (100 mL) and washed with 10 % NaOH (3 x 100 mL), dried ($MgSO_4$), and the solvent evaporated to give 1.8 g of the aminoquinoline, in 76 % yield; m.p. = 117-119° C; ^1H NMR ($CDCl_3$) δ 2.34 (s, 6H), 2.73 (t, 2H, *J*=5.5 Hz), 3.32 (m, 2H), 6.15 (br, 1H), 6.49 (d, 1H, *J*=5.4), 7.92 (d, 1H, *J*=9.2), 8.13 (dd, 1H, *J*=9.2, *J*=2.4), 8.65 (d, 1H, *J*=5.4), 8.80 (d, 1H, *J*=2.4); ^{13}C NMR ($CDCl_3$) δ 40.0, 45.1, 56.9, 101.1, 117.7, 122.0, 122.5, 125.9, 147.9, 148.0, 149.7, 153.3; IR ($CHCl_3$) 1352, 1546, 3388.

c. **N-(7-Nitroquinolin-4-yl)-N-(N,N-dimethylaminoethyl)-2-iodo-5,6-dimethoxybenzamide (8b).** Oxalyl chloride (1.5 mg, 12.0 mmol) was added to a solution of 3,4-dimethoxy-6-iodobenzoic acid (985 mg, 3.2 mmol) in anhydrous methylene chloride (30 mL), and the stirred mixture was refluxed for 3 hours. The mixture was then concentrated to dryness under reduced pressure. The acid chloride was redissolved in 20 mL of anhydrous methylene chloride, and this solution was added to a solution of **7b** (680 mg, 2.6 mmol) and triethylamine (2.0 g, 20.0 mmol) in methylene chloride (30 mL), and the resulting mixture was stirred at reflux for 2 hours. The reaction mix was cooled and washed with saturated sodium bicarbonate (3 x 75 mL), and extracted with 5 % aqueous HCl (4 x 100 mL). The combined aqueous extracts were basified with 30% NaOH and then extracted with chloroform (3 x 100 mL). Combined organic extracts were then dried ($MgSO_4$) and evaporated to give 760 mg of the amide, in 53 % yield; ^1H NMR ($CDCl_3$) δ 2.23 (s, 6H), 2.63 (m, 2H), 3.28 (s, 3H), 3.73 (s, 3H), 3.92 (m, 1H), 4.50 (m, 1H), 6.33 (s, 1H), 7.02 (s, 1H), 7.73 (d, 1H, *J*=4.8), 8.41 (m, 2H), 8.98 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 45.5, 47.5, 55.6, 56.1, 56.8, 82.9, 110.4, 120.6, 121.8, 124.1, 125.4, 126.6, 129.2, 133.3, 147.5, 148.4, 148.8, 149.9, 152.6, 153.1, 169.7; IR ($CHCl_3$) 1345, 1536, 1655.

Example 3: 8,9-Dimethoxy-3-nitro-5-[2-(N,N-dimethylamino)ethyl]-5*H*-dibenzo[*c*,*h*][1,6]naphthyridin-6-one (3c).



A mixture of compound **8c** (660 mg, 1.2 mmol), $Pd(OAc)_2$ (54 mg, 0.024 mmol), P(*o*-tolyl)$_3$ (147 mg, 0.048 mmol), and Ag_2CO_3 (660 mg, 2.4 mmol) in DMF (36 mL) was heated to reflux and stirred for 1 hour. The reaction mixture was cooled, diluted with chloroform and filtered through Celite, and the solvent was removed under vacuum. The crude residue was chromatographed in 99:1 chloroform-methanol, to provide 220 mg of the cyclized product, in 42% yield; m.p. = 232-234° C; ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 6H), 3.19 (t, 2H, *J*=7.2 Hz), 4.07 (s, 3H), 4.14 (s, 3H), 4.65 (t, 2H, *J*=7.2 Hz), 7.71 (s, 1H), 7.92 (s, 1H), 8.28 (d, 1H, *J*=9.2), 8.48 (dd, 1H, *J*=9.2, *J*=2.2), 9.64 (d, 1H, *J*=2.2), 9.68 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 46.1, 49.8, 56.4, 56.5, 57.4, 102.2, 108.9, 112.9, 118.1, 120.0, 122.2, 122.6, 126.8, 132.1, 142.1, 145.0, 148.9, 150.8, 151.3, 154.6, 163.4; IR ($CHCl_3$) 1341, 1518, 1658; HRMS calcd for $C_{22}H_{22}O_5N_4H$: 423.1668; found: 423.1663.

The intermediate compound **8c** was prepared as follows.

a. **4-Chloro-6-nitroquinoline (6c).** 4-Chloro-6-nitro was prepared from 4-hydroxy-6-nitroquinoline[3]. 4-Hydroxy-6-nitroquinoline (2.0 g, 10.5 mmol) was refluxed in $POCl_3$ (5 mL) for 5 hours. The reaction mix was cooled and poured onto ice. After complete hydrolysis of phosphoryl chloride, the mixture neutralized by addition of solid sodium acetate, and then extracted into

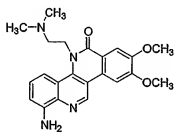
chloroform (3 x 125 mL), washed with water (3 x 100 mL), dried ($MgSO_4$), and the solvent evaporated *in vacuo*, and the product chromatographed in 9:1 hexanes-ethyl acetate, to give 1.6 g of the chloroquinoline, in 73 % yield; m.p. = 144-145° C (lit. m.p. = 144-145° C); ^1H NMR ($CDCl_3$) δ 7.68 (d, 1H, J=4.7), 8.29 (d, 1H, J=9.2), 8.55 (dd, 1H, J=9.2, J=2.6), 8.98 (d, 1H, J=4.7), 9.20 (d, 1H, J=2.6); ^{13}C NMR ($CDCl_3$) δ 121.4, 123.0, 123.9, 126.0, 132.1, 144.6, 146.5, 151.1, 153.3.

b. N'-(6-Nitroquinolin-4-yl)-N,N-dimethylethane-1,2-diamine (7c). Compound **6c** (750 mg, 3.6 mmol) was heated to reflux in N,N-dimethylethylenediamine (6.25 g, 70.9 mmol) with stirring for 2h, then cooled and the solvent was evaporated *in vacuo*. The crude residue was dissolved in 5 % aqueous HCl (100 mL) and washed with chloroform (3 x 100mL), and then basified with 30 % NaOH, extracted into ethyl acetate (7 x 100 mL), washed with water (2 x 150 mL), dried ($MgSO_4$), and the solvent evaporated to provide 890 mg, in 95 % yield; m.p. = 127-129° C; ^1H NMR ($CDCl_3$) δ 2.36 (s, 6H), 2.73 (t, 2H, J=5.9 Hz), 3.32 (m, 2H), 6.30 (br, 1H), 6.50 (d, 1H, J=5.5), 8.04 (d, 1H, J=9.2), 8.40 (dd, 1H, J=9.2, J=2.3), 8.66 (d, 1H, J=5.5), 8.89 (d, 1H, J=2.3); ^{13}C NMR ($CDCl_3$) δ 40.1, 45.2, 56.9, 100.3, 117.9, 118.0, 122.7, 131.3, 143.8, 151.4, 151.5, 154.3; IR ($CHCl_3$) 1342, 1513, 3381.

c. N-(6-Nitroquinolin-4-yl)-N-(N,N-dimethylaminoethyl)-2-iodo-5,6-dimethoxybenzamide (8c). Oxalyl chloride (1.5 g, 12.0 mmol) was added to a solution of 3,4-dimethoxy-6-iodobenzoic acid (985 mg, 3.2 mmol) in anhydrous methylene chloride (20 mL), and the stirred mixture was refluxed for 3 hours. The mixture was then concentrated to dryness under reduced pressure. The acid chloride was redissolved in 20 mL of anhydrous methylene chloride, and this solution was added to a solution of **7c** (700 mg, 2.7 mmol) and triethylamine (2.0 g, 20.0 mmol) in methylene chloride (30 mL), and the resulting mixture was stirred at reflux for 2 hours. The reaction mix was cooled and washed with

saturated sodium bicarbonate (3 x 75 mL), and extracted with 5 % aqueous HCl (4 x 100 mL). The combined aqueous extracts were basified with 30% NaOH and then extracted with chloroform (3 x 100 mL). Combined organic extracts were then dried ($MgSO_4$) and evaporated to give 1.15 g of the amide, in 78 % yield; ^1H NMR ($CDCl_3$) δ 2.23 (s, 6H), 2.63 (m, 2H), 3.35 (s, 3H), 3.71 (s, 3H), 3.96 (m, 1H), 4.29 (m, 1H), 6.50 (s, 1H), 6.94 (s, 1H), 7.79 (d, 1H, *J*=5.2), 8.22 (d, 1H, *J*=9.2), 8.48 (d, 1H, *J*=9.2), 9.0 (d, 1H, *J*=5.2), 9.28 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 45.5, 48.0, 55.6, 56.1, 56.8, 82.3, 110.7, 120.9, 121.5, 122.9, 123.4, 125.5, 132.2, 133.7, 145.9, 148.4, 149.1, 149.8, 151.5, 154.1, 169.7; IR ($CHCl_3$) 1345, 1535, 1655.

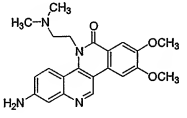
Example 4: 1-Amino-8,9-dimethoxy-5-[2-(N,N-dimethylamino)ethyl]-5*H*-dibenzo[*c,h*][1,6]naphthyridin-6-one (4a).



A mixture of $SnCl_2 \cdot 2\,H_2O$ (150 mg, 0.66 mmol) and granular tin (5 mg, .042 mmol) in ethanol (1.0 mL) and concentrated HCl (2.0 mL) was cooled to 0 °C and **3a** (40 mg, 0.09 mmol) was added in small portions. With stirring the starting material completely dissolved, and stirring was continued from 20 minutes at 0 °C and then for 4 hours at room temperature. Water (5 mL) was added and the mixture was neutralized by addition of solid sodium bicarbonate, and then the mixture was extracted with chloroform (6 x 10 mL), washed with water (3 x 10 mL), dried ($MgSO_4$), and evaporated under vacuum to give 30 mg of the reduced amino compound, in 81 % yield; mp 226-229 °C; ^1H NMR

($CDCl_3$) δ 2.35 (s, 6H), 3.03 (t, 2H, *J*=7.3), 4.08 (s, 3H), 4.14 (s, 3H), 4.78 (t, 2H, *J*=7.3), 6.99 (dd, 1H, *J*=7.8, *J*=1.2), 7.40 (dd, 1H, *J*=8.4, *J*=7.8), 7.73 (s, 1H), 7.75 (dd, 1H, *J*=8.4, *J*=1.2), 7.92 (s, 1H), 9.43 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 45.7, 46.7, 56.3, 56.3, 57.5, 102.1, 108.8, 110.5, 112.4, 113.0, 119.4, 119.7, 126.8, 127.7, 138.4, 141.1, 142.5, 144.8, 150.5, 154.2, 164.0; IR ($CDCl_3$) 1648, 3495; UV (THF) λ_{max} = 220, 252, 276, 314, 270 (log ε = 4.15, 4.37, 4.36, 4.34, 3.94); HRMS calcd for $C_{22}H_{24}O_3N_4H$: 393.1927; found: 393.1923.

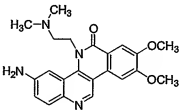
Example 5: 2-Amino-8,9-dimethoxy-5-[2-(N,N-dimethylamino)ethyl]-5*H*-dibenzo[*c,h*][1,6]naphthyridin-6-one (4b).



A mixture of $SnCl_2 \cdot 2\ H_2O$ (100 mg, 0.44 mmol) and granular tin (3 mg, .025 mmol) in ethanol (0.34 mL) and concentrated HCl (0.66 mL) was cooled to 0 °C and **3b** (17 mg, 0.04 mmol) was added in small portions. With stirring the starting material completely dissolved, and stirring was continued from 20 minutes at 0 °C and then for 10 hours at room temperature. During the course of the reaction the product precipitated from solution as a yellow solid. Water (2 mL) was added and the mixture was neutralized by addition of solid sodium bicarbonate, and then the mixture was extracted with chloroform (6 x 10 mL), washed with water (3 x 10 mL), dried ($MgSO_4$), and evaporated under vacuum to give 10 mg of the reduced amino compound, in 63 % yield; mp 208-210 °C; ^1H NMR ($CDCl_3$) δ 2.37 (s, 6H), 3.04 (t, 2H, *J*=7.4), 4.06 (s, 3H), 4.12 (s, 3H), 4.69 (t, 2H, *J*=7.4), 7.04 (dd, 1H, *J*=9.1, *J*=2.5), 7.32 (d, 1H, *J*=2.5), 7.67 (s, 1H), 7.89 (s, 1H), 8.35 (d, 1H, *J*=9.1), 9.42 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 45.9, 48.8, 56.3, 56.3, 57.6, 101.7, 108.8, 109.8, 110.9, 111.9, 117.2, 118.7, 126.1, 128.2,

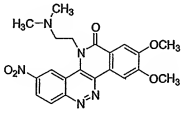
141.4, 146.1, 147.3, 150.0, 150.9, 154.3, 163.9; IR ($CDCl_3$) 1651, 3408; UV (THF) λ_{max} = 216, 256, 288, 342 (log ϵ = 3.82, 4.15, 4.33, 3.89); HRMS calcd for $C_{22}H_{24}O_3N_4H$: 393.1927; found: 393.1916.

Example 6: 3-Amino-8,9-dimethoxy-5-[2-(N,N-dimethylamino)ethyl]-5*H*-dibenzo[*c*,*h*][1,6]naphthyridin-6-one (4c).



A mixture of $SnCl_2 \cdot 2\ H_2O$ (100 mg, 0.44 mmol) and granular tin (3 mg, .025 mmol) in ethanol (0.34 mL) and concentrated HCl (0.66 mL) was cooled to 0 °C and **3c** (26 mg, 0.06 mmol) was added in small portions. With stirring the starting material completely dissolved, and stirring was continued from 20 minutes at 0 °C and then for 2 hours at room temperature. During the course of the reaction the product precipitated from solution as a bright yellow solid material. Water (2 mL) was added and the mixture was neutralized by addition of solid sodium bicarbonate, and then the mixture was extracted with chloroform (6 x 10 mL), washed with water (3 x 10 mL), dried ($MgSO_4$), and evaporated under vacuum to give 17 mg of the reduced amino compound, in 71 % yield; mp 213-215 °C; ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 6H), 3.06 (t, 2H, *J*=7.0), 4.07 (s, 3H), 4.13 (s, 3H), 4.68 (t, 2H, *J*=7.0), 7.18 (dd, 1H, *J*=8.8, *J*=2.4), 7.72 (s, 1H), 7.76 (d, 1H, *J*=2.4), 7.91 (s, 1H), 7.99 (d, 1H, *J*=8.8), 9.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 45.9, 48.5, 56.3, 56.4, 58.1, 102.2, 106.2, 108.7, 112.2, 119.6, 120.3, 120.4, 127.8, 131.7, 139.1, 142.1, 143.6, 144.7, 150.4, 154.1, 163.9; IR ($CDCl_3$) 1646; UV (THF) λ_{max} = 250, 300 (log ϵ = 4.34, 4.39); HRMS calcd for $C_{22}H_{24}O_3N_4H$: 393.1927; found: 393.1928.

Example 7: 11-(2-Dimethylaminoethyl)-2,3-dimethoxy-9-nitro-11*H*-5,6,11-triazachrysen-12-one (12a).



The title compound was prepared from compound **11a** (220 mg, 0.4 mmol) using a procedure similar to that described in Example 1; (25% yield); reaction time 2 h; mp 262-264 °C (dec.); ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 6H), 3.20 (t, 2H, *J*=7.0), 4.11 (s, 3H), 4.20 (s, 3H), 4.70 (t, 2H, *J*=7.0), 7.89 (s, 1H), 8.59 (dd, 1H, *J*=9.2, *J*=1.8), 8.69 (s, 1H), 8.78 (d, 1H, *J*=9.0), 9.91 (d, 1H, *J*=1.8); ^{13}C NMR ($CDCl_3$) δ 46.1, 48.2, 56.5, 56.8, 57.3, 104.5, 108.1, 115.0, 120.0, 122.0, 123.1, 128.5, 131.5, 133.2, 135.4, 147.7, 149.9, 152.4, 154.9, 162.4; IR ($CHCl_3$) 1347, 1533, 1663; HRMS calcd for $C_{21}H_{22}N_5O_5H$: 424.1621; found: 424.1616.

The intermediate compound **11a** was prepared as follows.

a. 4-Phenyloxy-6-nitrocinnoline (9a). 6-Nitro-4-phenoxycinnoline. As 4-chloro-6-nitrocinnoline (**9b**) is unstable, it was converted *in situ* to 4-phenoxy-6-nitrocinnoline **9a**, as described by Barber, H.J., et al., *J. Chem. Soc.*, Sec. C., 1967, *17*, 1657. 4-Phenoxy-6-nitrocinnoline can be isolated and is a useful intermediate for the preparation of **10a**. A mixture of 4-hydroxy-6-nitrocinnoline (5.78 g, 32.1 mmol), thionyl chloride (18.4 g, 155 mmol), and phosphorus pentachloride (592 mg, 2.8 mmol) in *o*-dichlorobenzene (120 mL) was stirred at reflux for 3 hours, during which time the solution became clear. The mixture was cooled to room temperature, and the solvent was carefully removed under vacuum (prolonged exposure of the crude product to vacuum

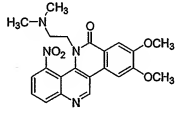
resulted in charring and substantially lower yield). Meanwhile, sodium phenoxide was prepared by heating a mixture of phenol (63.0 g, 0.67 mol) and sodium amide (1.5 g, 38.5 mmol) in benzene (75 mL) to reflux for 30 minutes. The crude, freshly dried 4-chlorocinnoline was dissolved in a minimum amount of anhydrous methylene chloride (~50 mL), and added to the cooled benzene solution of sodium phenoxide. The resulting mixture was concentrated under vacuum to remove all benzene and methylene chloride. The mixture was heated to 95 °C for 1 hour, and was poured into 10% NaOH (350 mL) and extracted with chloroform (7 x 200 mL). The combined extracts were washed with 10% NaOH (2 x 150 mL), dried ($MgSO_4$), evaporated, and the residue was triturated with boiling ethanol and filtered to provide 2.95 g of **9a**, in 35% combined yield for the two steps; ^1H NMR ($CDCl_3$) δ 7.29 (m, 2H), 7.45 (m, 1H), 7.60 (m, 2H), 8.68 (m, 2H), 8.89 (s, 1H), 9.34 (m, 1H).

b. **N'-(6-Nitrocinnolin-4-yl)-N,N-dimethylethane-1,2-diamine (10a).** A mixture of **9a** (2.0 g, 7.5 mmol) and N,N-dimethylethylenediamine (1.33 g, 15.2 mmol) in DMF (20 mL) was heated to 90 °C with stirring for 1h. Then the mixture was cooled and the solvent was removed under vacuum. The residue was partitioned between 10% NaOH (150 mL) and $CHCl_3$ (100 mL), and the aqueous phase was extracted with $CHCl_3$ (4 x100 mL). The combined organic extracts were washed with 10% NaOH (2 x 150 mL), dried ($MgSO_4$), and evaporated under vacuum, yielding 1.4 g, in 72% yield; mp 200-202 °C; IR ($CHCl_3$) 1345, 1518, 3349; ^1H NMR ($CDCl_3$) δ 2.36 (s, 3H), 2.77 (t, 2H, J=5.9), 3.54 (m, 2H), 6.87 (br, 1H), 8.40 (m, 2H), 8.82 (s, 1H), 8.95 (d, 1H, J=1.8); ^{13}C NMR ($CDCl_3$) δ 40.0, 45.2, 56.7, 114.5, 118.2, 123.5, 130.4, 131.4, 141.5, 145.7, 149.3; HRMS calcd for $C_{12}H_{15}N_5O_2$: 261.1226; found: 261.1233.

c. **N-(6-Nitrocinnolin-4-yl)-N-(N,N-dimethylaminoethyl)-2-iodo-4,5-dimethoxybenzamide (11a).** Oxalyl chloride (3.0 g, 23.2 mmol) was added to a mixture of 2-iodo-4,5-dimethoxybenzoic acid (1.5 g, 4.9 mmol) in methylene

chloride (40 mL), and the stirred mixture was heated to reflux under nitrogen for 4 h. The mixture was concentrated under reduced pressure and the acid chloride was redissolved in methylene chloride (40 mL) and added to a mixture of 10a (1.0 g, 4.0 mmol) and TEA (2.5 g, 25.0 mmol) in methylene chloride (40 mL). The resulting mixture was heated to reflux overnight and then cooled and washed with saturated sodium bicarbonate (3 x 100 mL) and brine (150 mL), dried ($MgSO_4$) and evaporated, and the residue was chromatographed in 99:1 $CHCl_3$-MeOH to provide 590 mg as a glue, in 29% yield; IR ($CHCl_3$) 1654; ^1H NMR ($CDCl_3$) δ 2.11 (s, 6H), 2.58 (m, 2H), 3.40 (s, 3H), 3.64 (s, 3H), 3.85 (m, 1H), 4.16 (m, 1H), 6.51 (s, 1H), 6.85 (s, 1H), 8.50 (m, 1H), 8.60 (m, 1H), 9.28 (s, 1H), 9.61 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 45.2, 48.1, 52.3, 56.2, 57.0, 82.5, 111.3, 121.0, 121.7, 123.8, 124.3, 131.0, 132.7, 138.2, 145.8, 148.8, 148.0, 150.2, 151.4, 169.6; HRMS calcd for $C_{21}H_{23}IN_5O_5H$: 552.0744; found: 552.0743.

Example 8 **8,9-Dimethoxy-4-nitro-5-[2-(N,N-dimethylamino)ethyl]-5*H*-dibenzo[*c*,*h*][1,6]-naphthyridin-6-one (3d).**



Prepared from **8d** (880 mg, 1.6 mmol), reaction time 1 h. Chromatograpic purification of the crude product using 98:2 chloroform/methnol gave 325 mg (48%) of the **3d** as an orange solid; mp 194-195 °C; ^1H NMR ($CDCl_3$) δ 1.75 (s, 6H), 2.30 (dd, 2H, J=6.9, J=5.4), 3.96 (dt, 1H, J=12.9, J=6.9), 4.10 (s, 3H), 4.16 (s, 3H), 4.74 (dt, 1H, J=12.9, J=5.4), 7.71 (s, 1H), 7.76 (dd, 1H, J=8.3, J=7.7), 7.95 (s, 1H), 8.29 (dd, 1H, J=7.7, J=1.4), 8.34 (dd, 1H, J=8.3,

J=1.4), 9.57 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 45.0, 47.5, 56.4, 56.5, 57.0, 102.5, 109.3, 110.8, 114.8, 120.7, 124.3, 126.1, 127.1, 135.7, 139.3, 146.8, 147.7, 148.8, 151.2, 154.3, 161.6; HRMS calcd for $C_{22}H_{22}O_3N_4H$: 423.1668; found: 423.1668.

The intermediate compound **8d** was prepared as follows.

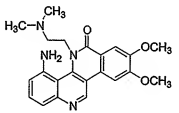
a. **4-Chloro-8-nitroquinoline (6a) and 4-chloro-5-nitroquinoline (6d).** 4-Chloroquinoline (10.0 g, 61.3 mmol) was added in small portions to sulfuric acid (45 mL) taking care to maintain the temperature at or below 15 °C. Then the solution was cooled and maintained at –5 °C during the addition of fuming nitric acid (9 mL). The mixture was allowed to warm to room temperature and stirred for an additional 3 h. The reaction mix was poured on ice and basified (pH 9) with NH_4OH. The resulting precipitate was filtered, washed well with water, dried, and recrystallized from methanol to provide 7.5 g (59%) of **6a** as golden-brown needles; mp 128-129 °C (lit.[32] mp 129-130 °C); ^{1}H NMR ($CDCl_3$) δ 7.67 (d, 1H, J=4.5), 7.75 (dd, 1H, J=8.6, J=7.6), 8.10 (dd, 1H, J=7.6, J=1.3), 8.48 (dd, 1H, J=8.6, J=1.3), 8.94 (d, 1H, J=4.5); ^{13}C NMR ($CDCl_3$) δ 123.0, 124.4, 126.5, 127.5, 128.3, 140.6, 143.2, 148.7, 152.1. The mother liquor was evaporated and chromatographed in 19:1 hexanes-ethyl acetate, to provide 2.05 g (16%) of the 5-nitro isomer **6d** as a very light yellow solid; mp 144-146 °C (lit.[31] mp 150 °C); ^{1}H NMR ($CDCl_3$) δ 7.65 (d, 1H, J=4.7), 7.82 (m, 2H), 8.35 (dd, 1H, J=2.5, J=7.3), 8.90 (d, 1H, J=4.7); ^{13}C NMR ($CDCl_3$) δ 118.2, 123.4, 125.1, 128.8, 134.2, 135.6, 139.1, 149.7, 151.2.

b. 4-[[2-(Dimethylamino)ethyl]amino]-5-nitroquinoline (7d). Compound **7d** was prepared from compound **6d** (800 mg, 3.84 mmol) and N,N-dimethylethylenediamine (6.25 g, 70.9 mmol), using a procedure similar to that described in Example 1, sub-part b, reaction time 90 min, providing 730 mg (73%) of **7d**, as an oily semi-solid; ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 6H), 2.64 (t, 2H,

J=5.9), 3.24 (m, 2H), 5.93 (br, 1H), 6.59 (d, 1H, 5.3), 7.62 (m, 2H), 8.17 (dd, 1H, *J*=5.0, *J*=4.8), 8.62 (d, 1H, *J*=5.3); ^{13}C NMR ($CDCl_3$) δ 41.1, 45.0, 56.7, 102.6, 110.9, 121.3, 127.1, 134.6, 135.6, 148.7, 149.8, 151.8.

c. **N-(5-Nitroquinolin-4-yl)-N-[2-(N,N-dimethylamino)ethyl]-2-iodo-4,5-dimethoxybenzamide (8d).** The acid chloride prepared from 3,4-dimethoxy-6-iodobenzoic acid (985 mg, 3.2 mmol) was redissolved in 30 mL of anhydrous methylene chloride, and this solution was added to a solution of **7d** (500 mg, 1.9 mmol) and triethylamine (2.0 g, 20.0 mmol) in methylene chloride (20 mL), and the resulting mixture was stirred at reflux for 2 h to provide 1.17 g (81%) of **8d** as a gum. The material was obtained as a mixture of atropisomers and was used as such without separation or further purification; HRMS calcd for $C_{22}H_{23}O_5N_4IH$: 551.0792; found: 551.0791.

Example 9. 4-Amino-8,9-dimethoxy-5-[2-(N,N-dimethylamino)ethyl]-5*H*-dibenzo[*c*,*h*][1,6]-naphthyridin-6-one (4d).



To a stirred solution of compound **3d** (37 mg, 0.088 mmol) in ethanol (8 mL) was added 1 pinch of Raney Nickel and 5 drops of hydrazine hydrate, and the mixture was stirred at ambient temperature for 2 h. The mixture was filtered through Celite and the filtrate was evaporated. The residue was dissolved in chloroform (25 mL) and washed with brine (25 mL), dried ($MgSO_4$), and evaporated, giving 28 mg (81%) as a yellow solid; mp 239-241 °C; ^{1}H NMR ($CDCl_3$) δ 1.80 (s, 6H), 2.10 (m, 2H), 4.05 (s, 3H), 4.13 (s, 3H), 4.48 (m, 3H), 5.07 (m, 1H), 6.79 (dd, 1H, *J*=6.3, *J*=2.5), 7.52 (m, 2H), 7.64 (s, 1H), 7.87 (s,

1H), 9.38 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 45.1, 50.5, 56.3, 56.4, 57.4, 102.0, 109.1, 109.6, 111.3, 112.6, 118.7, 119.5, 127.7, 130.0, 141.0, 142.6, 144.8, 149.8, 150.0, 154.3, 164.5; HRMS calcd for $C_{22}H_{24}O_3N_4H$: 393.1927; found: 393.1925.

Example 10 The following illustrate representative pharmaceutical dosage forms, containing a compound of formula I ('Compound X'), for therapeutic or prophylactic use in humans.

(i) Tablet 1	mg/tablet
'Compound X'	100.0
Lactose	77.5
Povidone	15.0
Croscarmellose sodium	12.0
Microcrystalline cellulose	92.5
Magnesium stearate	3.0
	300.0

(ii) Tablet 2	mg/tablet
'Compound X'	20.0
Microcrystalline cellulose	410.0
Starch	50.0
Sodium starch glycolate	15.0
Magnesium stearate	5.0
	500.0

(iii) Capsule	mg/capsule
'Compound X'	10.0
Colloidal silicon dioxide	1.5
Lactose	465.5
Pregelatinized starch	120.0
Magnesium stearate	3.0
	600.0

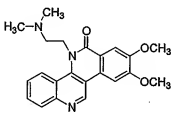
(iv) Injection 1 (1 mg/ml)	mg/ml
'Compound X' (free acid form)	1.0
Dibasic sodium phosphate	12.0
Monobasic sodium phosphate	0.7
Sodium chloride	4.5
1.0 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

(v) Injection 2 (10 mg/ml)	mg/ml
'Compound X' (free acid form)	10.0
Monobasic sodium phosphate	0.3
Dibasic sodium phosphate	1.1
Polyethylene glycol 400	200.0
01 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

(vi) Aerosol	mg/can
'Compound X'	20.0
Oleic acid	10.0
Trichloromonofluoromethane	5,000.0
Dichlorodifluoromethane	10,000.0
Dichlorotetrafluoroethane	5,000.0

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art.

Comparative Example 1:



8,9-Dimethoxy-5-[2-(N,N-dimethylamino)ethyl]-*5H*-dibenzo[*c,h*]1,6-naphthyridin-6-one (5). A mixture of compound **8d** (606 mg, 1.2 mmol), $Pd(OAc)_2$ (54 mg, 0.024 mmol), P(*o*-tolyl)$_3$ (147 mg, 0.048 mmol), and Ag_2CO_3 (660 mg, 2.4 mmol) in DMF (36 mL) was heated to reflux and stirred for 25 minutes. The reaction mixture was cooled, diluted with chloroform and filtered through Celite, and the solvent was removed under vacuum. The crude residue was chromatographed in 99:1 chloroform-methanol, to provide 189 mg of the cyclized product, in 42 % yield; mp 202.5-203.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 6H), 3.01 (t, 2H, *J*=7.2 Hz), 4.04 (s, 3H), 4.11 (s, 3H), 4.69 (t, 2H, *J*=7.2 Hz),

7.58 (m, 1H), 7.67 (s, 1H), 7.71 (m, 1H), 7.87 (s, 1H), 8.16 (d, 1H, *J*=8.0), 8.47 (d, 1H, *J*=8.8), 9.51 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 45.8, 48.9, 56.3, 56.3, 57.6, 102.1, 108.8, 111.8, 118.9, 119.6, 124.6, 125.9, 127.5, 129.1, 130.5, 140.8, 145.6, 148.7, 150.5, 154.2, 163.7; IR ($CHCl_3$) 1650; UV (THF) λ_{max} = 250, 286, 336 (log ϵ = 4.39, 4.42, 4.03);

The intermediate compound **8d** was prepared as follows.

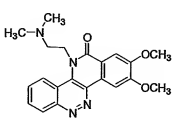
a. Synthesis of **4-Chloroquinoline (6d).** 4-Quinolone (10.0 g, 69.0 mmol) was added to phosphorus oxychloride (82.3 g, 0.537 mol), and the stirred mixture was heated to reflux, and maintained at this temperature for 20 minutes. The reaction mixture was then cooled, and ice was slowly added to the crude residue until the evolution of HCl gas was no longer observed. The mixture was then neutralized by addition of 10% NaOH (pH 7.0) and then extracted into $CHCl_3$ (3 x 100 mL), washed with water (3 x 100 mL), dried ($MgSO_4$), and evaporated to give 10.34 g of the chloroquinoline, in 92 % yield; mp 28-29 °C (lit mp 29-32 °C); ^{1}H NMR ($CDCl_3$) δ 7.50 (d, 1H, *J*=4.6), 7.65 (ddd, 1H, *J*=8.4, *J*=7.0, *J*=1.2), 7.78 (ddd, 1H, *J*=8.4, *J*=7.0, *J*=1.4), 8.14 (dd, 1H, *J*=8.4, *J*=1.4), 8.24 (dd, 1H, *J*=8.4, *J*=1.2), 8.79 (d, 1H, *J*=4.6); ^{13}C NMR ($CDCl_3$) δ 121.4, 124.3, 126.7, 127.7, 130.0, 130.5, 142.7, 129.3, 149.9.

b. Synthesis of **4-[[2-(Dimethylamino)ethyl]amino]quinoline (7d).** Compound **6d** (2.3 g, 14.1 mmol) was stirred in boiling phenol (12.0 g, 128 mmol) for 2.5 hours. Then the mixture was cooled to 100 °C and N,N-dimethylethylenediamine (3.0 g, 30.0 mmol) was added, and the reaction was stirred for an additional 16 hours. The reaction mixture was cooled and solvent removed under vacuum. The residue was dissolved in chloroform (150 mL) and washed with 10 % NaOH (3 x 75 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give 2.88 g, in 96 % yield; mp 99.5- 100 °C; ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 6H), 2.65 (t, 2H, *J*=6.0), 3.26 (m, 2H), 5.95 (br, 1H), 6.36 (d, 1H, *J*=5.2), 7.41 (ddd,

1H, *J*=8.3, *J*=6.9, *J*=1.0), 7.60 (ddd, 1H, *J*=8.5, *J*=6.9, *J*=1.2), 7.81 (dd, 1H, *J*=8.3, *J*=1.2), 7.97 (dd, 1H, *J*=8.5, *J*=1.0), 8.54 (d, 1H, *J*=5.2); ^{13}C NMR ($CDCl_3$) δ 40.1, 45.1, 57.2, 98.9, 119.1, 119.9, 124.5, 129.0, 129.8, 148.5, 150.0, 151.1;

c. Synthesis of **N-(quinolin-4-yl)-N-(N,N-dimethylaminoethyl)-2-iodo-5,6-dimethoxybenzamide (8d).** Oxalyl chloride (2.1 g, 16.2 mmol) was added to a solution of 3,4-dimethoxy-6-iodobenzoic acid (1.5 g, 4.87 mmol) in anhydrous methylene chloride (40 mL), and the stirred mixture was refluxed for 4 hours. The mixture was then concentrated to dryness under reduced pressure. The acid chloride was redissolved in 40 mL of anhydrous methylene chloride, and this solution was added to a solution of **7d** (870 mg, 4.05 mmol) and triethylamine (4.0 g, 40.0 mmol) in methylene chloride (30 mL), and the resulting mixture was stirred at reflux for 2 hours. The reaction mix was cooled and washed with saturated sodium bicarbonate (3 x 75 mL), and extracted with 5 % aqueous HCl (4 x 100 mL). The combined aqueous extracts were basified with 30% NaOH and then extracted with chloroform (3 x 75 mL). Combined organic extracts were then dried ($MgSO_4$) and evaporated to give 1.45 g of the amide, in 73 % yield; ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 6H), 2.63 (m, 2H), 3.07 (s, 3H), 3.68 (s, 3H), 3.93 (m, 1H), 4.62 (m, 1H), 6.26 (s, 1H), 7.00 (s, 1H), 7.44 (d, 1H, *J*=4.4), 7.69 (m, 2H), 8.11 (m, 2H), 8.75 (d, 1H, *J*=4.4); ^{13}C NMR ($CDCl_3$) δ 45.6, 47.0, 55.3, 56.0, 56.7, 82.5, 110.2, 121.6, 122.8, 125.8, 127.6, 130.0, 130.5, 130.6, 133.8, 146.9, 148.1, 149.6, 149.8, 150.8, 169.8; IR ($CHCl_3$) 1650;

Comparative Example 2:



11-(2-Dimethylaminoethyl)-2,3-dimethoxy-11*H*-5,6,11-triazachrysen-12-one (12b). A mixture of **11b** (150 mg, 0.3 mmol), $Pd(OAc)_2$ (13.5 mg, 0.06 mmol), P(*o*-tolyl)$_3$ (37 mg, 0.12 mmol), and Ag_2CO_3 (165 mg, 0.3 mmol) in DMF (9 mL) was heated to reflux and stirred for 25 minutes. The reaction mixture was cooled, diluted with chloroform and filtered through Celite, and the solvent was removed under vacuum. The crude residue was chromatographed in 99:1 chloroform-methanol, to provide 45 mg of the cyclized product, in 40 % yield; mp 218-219 °C; ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 6H, 3.06 (t, 2H, J=7.5), 4.09 (s, 3H), 4.19 (s, 3H), 4.76 (t, 2H, J=7.5), 7.85 (m, 3H), 8.67 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 45.9, 47.3, 56.4, 56.7, 57.4, 104.5, 108.0, 116.1, 119.8, 123.6, 129.2, 129.6, 130.4, 130.5, 131.4, 134.2, 150.0, 151.7, 154.6, 162.8; IR ($CHCl_3$) 1655; UV (THF) λ_{max} = 146, 288, 340 (log ϵ = 4.33, 4.39, 4.04).

The intermediate compound **11b** was prepared as follows.

a. 4-Chlorocinnoline (9b). A mixture of 4-hydroxycinnoline (2.0 g, 13.7 mmol), phosphorus oxychloride (1.94 mL, 20.5 mmol), and pyridine (0.33 mL, 4.1 mmol) in chlorobenzene (50 mL) was refluxed for 1 hour. Then the mixture was cooled and the solvent evaporated under vacuum, water was added, and the mixture was neutralized with solid sodium bicarbonate and extracted with chloroform (3 x 100 mL), washed with water (3 x 100 mL), dried ($MgSO_4$) and evaporated under vacuum, giving 1.84 g, in 82 % yield; mp 76-77 °C (lit mp 78 °C); ^{1}H NMR ($CDCl_3$) δ 7.91 (m, 2H), 8.20 (dd, 1H, *J*=6.2, *J*=2.1), 8.57 (dd, 1H, *J*=6.6, *J*=1.8), 9.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 123.0, 124.9, 130.2, 131.6, 132.3, 133.8, 134.9, 144.4.

b. 4-[[2-(Dimethylamino)ethyl]amino]cinnoline (10b). Intermediate **9b** (1.0 g, 6.1 mmol) was stirred in neat refluxing N,N-dimethylethylenediamine (6.25 g, 70.9 mmol) for 3 hours, then the mixture was cooled and the solvent

evaporated under reduced pressure. The crude material was partitioned between water (100 mL) and chloroform (100 mL), and the aqueous phase was washed with chloroform (2 x 100 mL). The combined organic phases were washed with brine (75 mL) and dried ($MgSO_4$) and evaporated under vacuum, giving 890 mg, in 68 % yield; mp 146-148 °C; ^1H NMR ($CDCl_3$) δ 2.31 (s, 6H), 2.69 (t, 2H, J=5.9), 3.88 (m, 2H), 6.08 (br, 1H), 7.57 (ddd, 1H, J=8.3, J=7.4, J=0.8), 7.72 (ddd, 1H, J=8.4, J=7.4, J=0.6), 7.82 (dd, 1H, J=8.3, J=0.6), 8.30 (dd, J=8.4, J=0.8), 8.63 (s, 1H); 39.6, 45.1, 57.0, 115.8, 119.2, 128.2, 128.7, 129.5, 129.9, 139.9, 148.7.

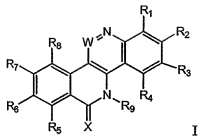
c. **N-(quinolin-4-yl)-N-(N,N-dimethylaminoethyl)-2-iodo-5,6-dimethoxybenzamide (11b).** Oxalyl chloride (2.1 g, 16.2 mmol) was added to a solution of 3,4-dimethoxy-6-iodobenzoic acid (1.5 g, 4.87 mmol) in anhydrous methylene chloride (40 mL), and the stirred mixture was refluxed for 4 hours. The mixture was then concentrated to dryness under reduced pressure. The acid chloride was redissolved in 40 mL of anhydrous methylene chloride, and this solution was added to a solution of **10b** (870 mg, 4.05 mmol) and triethylamine (4.0 g, 40.0 mmol) in methylene chloride (30 mL), and the resulting mixture was stirred at reflux overnight. The reaction mix was cooled and washed with saturated sodium bicarbonate (3 x 75 mL), and brine (75 mL), dried ($MgSO_4$) and evaporated, and the crude product mixture was chromatographed in 98:2 chloroform-methanol, to provide 165 mg of the desired amide, in 8 % yield; ^1H NMR ($CDCl_3$) δ 2.21 (s, 6H), 2.63 (m, 2H), 3.19 (s, 3H), 3.70 (s, 3H), 3.94 (m, 1H), 4.59 (m, 1H), 6.28 (s, 1H), 7.01 (s, 1H), 7.88 (m, 2H), 8.20 (dd, 1H, *J*=6.6, *J*=3.4), 8.54 (dd, 1H, *J*=6.6, *J*=3.0), 9.35 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 45.5, 47.3, 55.4, 56.1, 56.8, 82.9, 110.4, 121.9, 122.0, 123.8, 130.7, 131.0, 132.0, 133.0, 136.6, 145.2, 148.2, 149.9, 151.7, 169.9; IR ($CHCl_3$) 1658.

All publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The

invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

What is claimed is:

1. A compound of formula I:



I

wherein:

one of R_1, R_2, R_3, and R_4 is nitro or NR_aR_b;

and the remaining R_1, R_2, R_3, and R_4 are each independently hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, NR_aR_b, $COOR_c$, OR_d; or R_1 and R_2, R_2 and R_3, or R_3 and R_4 taken together are methylenedioxy, 1,2-ethylenedioxy, or 1,3-propylenedioxy;

R_5 is hydrogen, hydroxy, or fluoro;

each R_6, R_7, and R_8 is independently hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, NR_aR_b, $COOR_c$, OR_d; or R_6 and R_7, or R_7 and R_8 taken together are methylenedioxy, 1,2-ethylenedioxy, or 1,3-propylenedioxy;

R_9 is $(C_1\text{-}C_6)$alkyl substituted with one or more solubilizing groups;

W is N or CH;

X is two hydrogens, =O, =S, or $=NR_e$;

R_a and R_b are each independently hydrogen or $(C_1\text{-}C_6)$alkyl, or R_a and R_b together with the nitrogen to which they are attached form a pyrrolidino, piperidino or morpholino ring;

each R_c is hydrogen, $(C_1\text{-}C_6)$alkyl, aryl, or aryl$(C_1\text{-}C_6)$alkyl;

each R_d is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkanoyl, aryl, or aryl$(C_1\text{-}C_6)$alkyl; and R_e is hydrogen, $(C_1\text{-}C_6)$alkyl, aryl, or aryl$(C_1\text{-}C_6)$alkyl;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 wherein W is N.

3. The compound of claim 1 wherein W is CH.

4. The compound of any one of claims 1-3 wherein R_1 is nitro.

5. The compound of any one of claims 1-3 wherein R_1 is NR_aR_b.

6. The compound of any one of claims 1-5 wherein R_2, R_3, and R_4 are each independently hydrogen, or OR_d, wherein each R_d is hydrogen or (C_1-C_6)alkyl.

7. The compound of any one of claims 1-5 wherein R_2, R_3, and R_4 are each hydrogen.

8. The compound of any one of claims 1-3 wherein R_2 is nitro or NR_aR_b.

9. The compound of any one of claims 1-3 wherein R_2 is nitro.

10. The compound of any one of claims 1-3 wherein R_2 is NR_aR_b.

11. The compound of any one of claims 1-3 and 8-10 wherein R_1, R_3, and R_4 are each independently hydrogen, or OR_d, wherein each R_d is hydrogen or (C_1-C_6)alkyl.

12. The compound of any one of claims 1-3 and 8-10 wherein R_1, R_3, and R_4 are each hydrogen.

13. The compound of any one of claims 1-3 wherein R_3 is nitro or NR_aR_b.

14. The compound of any one of claims 1-3 wherein R_3 is nitro.

15. The compound of any one of claims 1-3 wherein R_3 is NR_aR_b.

16. The compound of any one of claims 1-3 and 13-15 wherein R_1, R_2, and R_4 are each independently hydrogen, or OR_d, wherein each R_d is hydrogen or (C_1-C_6)alkyl.

17. The compound of any one of claims 1-3 and 13-15 wherein R_1, R_2, and R_4 are each hydrogen.

18. The compound of any one of claims 1-3 wherein R_4 is nitro.

19. The compound of any one of claims 1-3 wherein R_4 is NR_aR_b.

20. The compound of any one of claims 1-3, 18, and 19 wherein R_1, R_2, and R_3 are each independently hydrogen, or OR_d, wherein each R_d is hydrogen or (C_1-C_6)alkyl.

21. The compound of any one of claims 1-3, 18, and 19 wherein R_1, R_2, and R_3 are each hydrogen.

22. The compound of any one of claims 1-3 wherein R_2 or R_3 is nitro or NR_aR_b.

23. The compound of any one of claims 1-22 wherein R_5 is hydrogen.

24. The compound of any one of claims 1-22 wherein R_5 is hydroxy or fluoro.

25. The compound of any one of claims 1-24 wherein each R_6, R_7, and R_8 is independently hydrogen, or OR_d.

26. The compound of any one of claims 1-24 wherein R_6 and R_7 are each independently OR_d, wherein each R_d is $(C_1$-$C_6)$alkyl; and R_8 is hydrogen.

27. The compound of any one of claims 1-24 wherein or R_6 and R_7 taken together are methylenedioxy, 1,2-ethylenedioxy, or 1,3-propylenedioxy; and R_8 is hydrogen.

28. The compound of any one of claims 1-27 wherein R_9 is $(C_1$-$C_6)$alkyl substituted with one or more hydroxy groups.

29. The compound of any one of claims 1-27 wherein R_9 is $(C_1$-$C_6)$alkyl substituted with one hydroxy group.

30. The compound of any one of claims 1-27 wherein R_9 is $(C_1$-$C_6)$alkyl substituted with one or more mercapto groups.

31. The compound of any one of claims 1-27 wherein R_9 is $(C_1$-$C_6)$alkyl substituted with one mercapto group.

32. The compound of any one of claims 1-27 wherein R_9 is $(C_1$-$C_6)$alkyl substituted with one or more carboxy groups.

33. The compound of any one of claims 1-27 wherein R_9 is $(C_1$-$C_6)$alkyl substituted with one carboxy group.

34. The compound of any one of claims 1-27 wherein R_9 is (C_1-C_6)alkyl substituted with one or more NR_fR_g groups.

35. The compound of any one of claims 1-27 wherein R_9 is (C_1-C_6)alkyl substituted with one NR_fR_g group.

36. The compound of any one of claims 1-27 wherein R_9 is (C_1-C_6)alkyl substituted with one or more NH_2 groups.

37. The compound of any one of claims 1-27 wherein R_9 is a (C_1-C_6)alkyl substituted with one NH_2 group.

38. The compound of any one of claims 1-27 wherein R_9 is (C_1-C_6)alkyl substituted with one or more $N(CH_3)_2$ groups.

39. The compound of any one of claims 1-27 wherein R_9 is a (C_1-C_6)alkyl substituted with one $N(CH_3)_2$ group.

40. The compound of any one of claims 1-27 wherein R_9 is (C_1-C_6)alkyl substituted with one or more $N(CH_2CH_3)_2$ groups.

41. The compound of any one of claims 1-27 wherein R_9 is a (C_1-C_6)alkyl substituted with one $N(CH_2CH_3)_2$ group.

42. The compound of any one of claims 1-27 wherein R_9 is a (C_1-C_6)alkyl substituted with one or more (C_1-C_6)alkoxycarbonyl, cyano, halo, hydroxy, mercapto, oxo, carboxy, nitro, pyrrolidinyl, piperidinyl, imidazolidinyl, imidazolinyl, piperazinyl, morpholinyl, thiomorpholinyl, or $-NR_fR_g$ groups, wherein R_f and R_g may be the same or different and are chosen from hydrogen, (C_1-C_6)alkyl, and (C_3-C_6)cycloalkyl.

43. The compound of any one of claims 1-27 wherein R_9 is a (C_2-C_4)alkyl substituted with one or two groups selected from hydroxy, mercapto, carboxy, amino, methylamino, ethylamino, dimethylamino, and diethylamino.

44. The compound of any one of claims 1-27 wherein R_9 is 2-hydroxyethyl.

45. The compound of any one of claims 1-27 wherein R_9 is 3-hydroxypropyl.

46. The compound of any one of claims 1-27 wherein R_9 is 2-hydroxypropyl.

47. The compound of any one of claims 1-27 wherein R_9 is $-CH_2CH_2-NR_fR_g$ wherein R_f and R_f are each independently hydrogen or (C_1-C_6)alkyl.

48. The compound of any one of claims 1-27 wherein R_9 is $-CH_2CH_2-NR_fR_g$ wherein R_f and R_f are each independently methyl or ethyl.

49. Any one of compounds **3a**, **3b**, **3c**, **4a**, **4b**, **4c**, and **12a**; or a pharmaceutically acceptable salt thereof.

50. The compound of claim 1 wherein R_1 is hydrogen; R_2 is hydrogen; R_3 is nitro; R_4 is hydrogen; R_5 is hydrogen; R_6 is methoxy; R_7 is methoxy; R_8 is hydrogen; and R_9 is 2-(*N,N*-dimethylamino)ethyl or 2-(*N,N*-diethylamino)ethyl; W is N or CH; and X is =O; or a pharmaceutically acceptable salt thereof.

51. A pharmaceutical composition comprising a compound as described in any one of claims 1-50 in combination with a pharmaceutically acceptable diluent or carrier.

52. A method of inhibiting cancer cell growth, comprising administering to a mammal afflicted with cancer, an amount of a compound as described in any one of claims 1-50, effective to inhibit the growth of said cancer cells.

53. A method comprising inhibiting cancer cell growth by contacting said cancer cell in vitro or in vivo with an amount of a compound as described in any one of claims 1-50, effective to inhibit the growth of said cancer cell.

54. A compound as described in any one of claims 1-50 for use in medical therapy.

55. The compound of claim 54 wherein the therapy is treating cancer.

56. The use of a compound as described in any one of claims 1-50 for the manufacture of a medicament useful for the treatment of cancer.

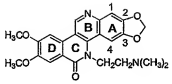
57. A method of producing an antibacterial effect in a mammal in need of such treatment comprising administering to the mammal, an amount of a compound as described in any one of claims 1-50, effective to provide an antibacterial effect.

58. A method of producing an antifungal effect in a mammal in need of such treatment comprising administering to the mammal, an amount of a compound as described in any one of claims 1-50, effective to provide an antifungal effect.

59. The use of a compound as described in any one of claims 1-50 for the manufacture of a medicament useful for producing an antibacterial, antifungal, antiprotozoal, antihelmetic, antipsoriatic, antipsoriatic, or antiviral effect in a mammal.

60. The use of a compound as described in any one of claims 1-50 for the manufacture of a medicament useful for producing an antifungal effect in a mammal.

Figure 1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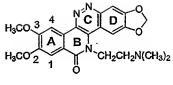
2
O
B
A
D
C
3
4
O
N
CH2CH2N(CH3)2
O

1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H3CO
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4
2
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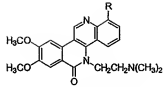
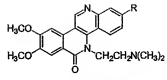
C
D
A
B
O
O
N
CH2CH2N(CH3)2
O

2

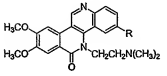
Figure 2



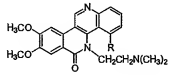
3a R = NO_2
4a R = NH_2



3b R = NO_2
4b R = NH_2



3c R = NO_2
4c R = NH_2



3d R = NO_2
4d R = NH_2

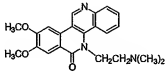


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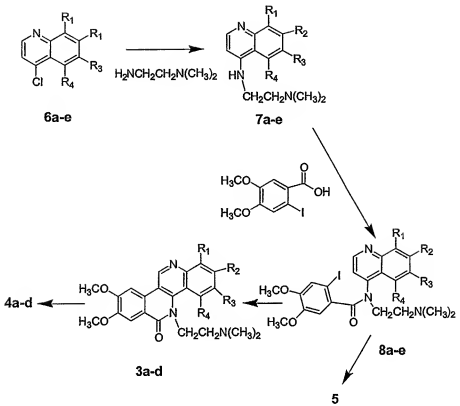
Figure 3


6a-e
7a-e
8a-e
3a-d
4a-d
5
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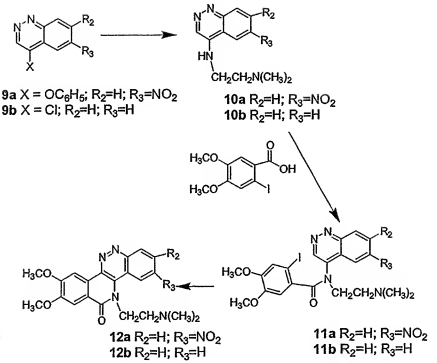
CH2CH2N(CH3)2
H3CO
OH
I
Cl

Figure 4


9a X = OC6H5; R2=H; R3=NO2
9b X = Cl; R2=H; R3=H
10a R2=H; R3=NO2
10b R2=H; R3=H
11a R2=H; R3=NO2
11b R2=H; R3=H
12a R2=H; R3=NO2
12b R2=H; R3=H